The end of nature
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FROM BANANA VACCINES TO FAST-GROWING FISH: DNA LETS SCIENTISTS PLAY GOD

by Mark Schoofs

the end of NATURE

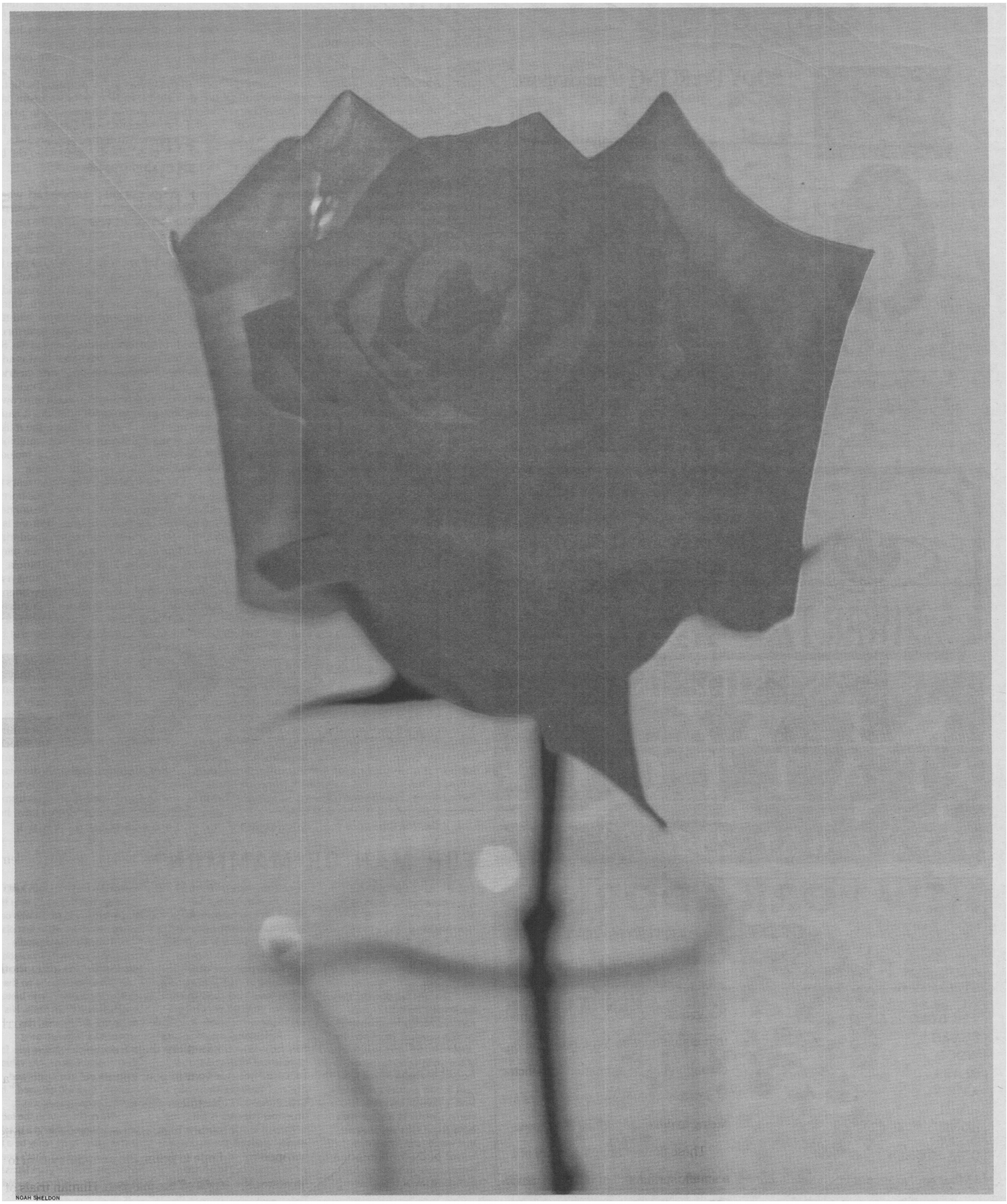
JIM: They're common as weeds, but—you—well, you're—Blue Roses!
LAURA: But blue is wrong for—roses....
—The Glass Menagerie

Tennessee Williams lived in an era when a blue rose was impossible, a symbol of something beyond unique. But genetic engineering will soon make that notion quaint. Already, a blue carnation has been created by splicing in a petunia gene, and researchers are racing to develop the first blue rose.

These flowers are harbingers of a scientific springtime in which all manner of flora and fauna emerge from biotech laboratories. The blue carnation was made through "transgenics," a process in which genes from one organism are transferred to another. This process has profound ramifications: No longer are genes confined within species; now they are infinitely interchangeable. In addition, an organism's own DNA can be rearranged, and genes not found in nature can be manufactured from scratch. Using these techniques, scientists have created:

▸ Self-shearing sheep, developed to facilitate wool gathering. These animals, injected with a genetically engineered hormone, never made it to market because they suffered health problems such as sunburn. But researchers are working on genetically altered sheep that would secrete a natural insect repellent in their sweat, creating moth-proof wool.

▸ Edible vaccines. Bacterial diarrhea kills more than 2 million children a year in poor countries. By splicing a harmless genetic fragment from the culprit bacteria into a banana, scientists hope to prime the immune system to fight off the infection. Human trials of the first edible vaccine, produced →



NOAH SHELDON

SCHOOFS

CONTINUED FROM PAGE 56

in a potato, began last month.

▶ Bacterial looms. By splicing in the gene from a silkworm, researchers have made bacteria spin thread that is supersoft and superstrong.

▶ High-nutrition crops. Using a synthetic gene not known to exist in nature, researchers have quintupled the protein content of sweet potatoes, an African and Asian staple. Scientists are also trying to add vitamin A to rice—which could prevent a quarter-million children from going blind—by inserting a daffodil gene. And scientists are making crops hardier, able to fight off disease, kill insect pests, and even grow in harsh soil.

▶ Harmless mosquitoes. Instead of vaccinating people, some researchers are trying to change the salivary glands of mosquitoes so that they can't transmit malaria and other diseases. The first success: mosquitoes with a gene that neutralizes the Dengue virus.

▶ Transplant organs. Using human genes, pigs have grown livers that could be medically transplanted into humans. The human genes coat the organs with proteins that "fool" the human immune system into believing the foreign organs are its own.

▶ Drug "pharms." Human proteins often make excellent drugs, such as insulin for diabetes. It's usually difficult to extract enough from human beings, but such drugs can be easily harvested from genetically engineered plants, animals, and even bugs that have had the medicinal gene spliced in. Goats, tobacco plants, and caterpillars have received genes that make them produce disease-fighting proteins, and more are on the way.

▶ Hot-blooded strawberries. By putting the antifreeze gene from Arctic fish into strawberries, other plants, and even other fish, researchers hope to make organisms that can withstand harsh winters and higher latitudes.

As astounding as these innovations seem, they represent only a toe in the water of genetic manipulation. Just 65 transgenic organisms have been licensed in the U.S. for commercial use, but in the last year alone more than 1000 field trials were conducted. So far, the vast majority of work has taken place in plants and bacteria, which are easier and cheaper to work with than animals. But that is about to change. "It used to cost $350,000 to $400,000 to produce one transgenic animal," says Michael Bishop, a molecular biologist with American Breeder Service Global, a livestock company. Now, he says, cloning and other advances have reduced the cost to "$50,000 or less."

What will the future hold? Biotech entrepreneur Elliot Entis is betting on a "blue revolution"—the marine equivalent of agriculture's green revolution, which kept billions from starving. Entis's company, A/F Protein, has produced a transgenic salmon that grows to harvest size in less than 18 months instead of the normal three years. But to Rita Colwell, president of the University of Maryland's Biotechnology Institute, fish that still swim seem passé. Scientists have long known how to produce "cell lines"—animal tissue that grows in petri dishes. Future fish farms, she predicts, will "grow vats of genetically engineered cell lines that will get shaped as fillets."

Something curious happened when a synthetic gene was inserted into the sweet potato. The protein content soared, but the new gene accounted for only a small fraction of this boost. Somehow, the sweet potato's natural protein genes shifted into high gear. How? Tuskegee University's C. S. Prakash, who helped develop this super sweet potato, chuckles, "We have no idea."

Not all surprises are so benign. One attempt to make salmon grow bigger had to be aborted because the genetic change deformed the heads of the fish, causing many to die. Similarly, when human growth hormone was added to pigs they developed swollen joints, gastric ulcers, and infertility. A genetically engineered growth hormone was also injected into cows to make them produce more milk, but it caused udder infections, leading to pus in the milk. In response, many farmers used extra antibiotics, but that only created other dangers, including the evolution of drug-resistant bacteria.

Such grotesque side effects stoke fears that genetic engineering will unleash some horrible calamity. This dread mixes fear of the unknown and mistrust of scientific hubris. So strong is the fear that Switzerland is currently considering a referendum to ban the use of genetically altered animals and crops. This may be paranoia, but there is real danger here. Orrey P. Young, a regulator with the United States Department of Agriculture, notes that genetically engineered organisms "have the potential for causing a disaster, wiping out an endangered species or portions of our food supply."

The main peril is ecological havoc. Just as scientists know very little about DNA, they also don't fully understand the larger biosystem into which they are releasing genetically altered organisms. For example, scientists used to believe the ocean didn't contain viruses. But in 1990, says Raymond Zilinskas, an associate professor at the University of Maryland's Biotechnology Institute, researchers discovered that "the surface layer of the ocean is packed with billions of viral particles." This has tremendous implications, because viruses have been

CONTINUED ON PAGE 61

FOR MAN OR MAMMON?

THE WORLD'S POPULATION, it has been noted, grows by a Mexico City every month, a Germany every year, a China every decade. Molecular genetics alone won't feed the human race, but it will make a major contribution.

Over the last decade, the Rockefeller Foundation has invested heavily in enhancing the genetic composition of rice, the staple crop for more than a third of the world's people. "If we increase the yield by just 5 per cent in only a quarter of the rice land in China," says Robert Herdt, director of Rockefeller's agricultural sciences program, that would feed an additional 22 million people. Herdt expects a "measurable impact" by 2001.

That impact could have come even sooner. "The best estimate is that about $2.5 billion per year is spent on agricultural biotech research," says Herdt, "but only about 50 to 70 million dollars is being directed to problems of the developing world." That amounts to less than 3 per cent. Where does the other 97 per cent go? To the pursuit of profit.

Agricultural conglomerates "are focused on crops with high commercial interest, such as corn and soybean and cotton," explains Tuskegee University's C. S. Prakash. "So the kind of investment needed is not going to happen in staples of the Third World." (Indeed, the largest slice of commercial field tests involves crops engineered to withstand herbicides. After spraying, the weeds die and the crops keep growing. But this won't help the many farmers in Africa who can't afford herbicides in the first place.)

Industry spokespeople argue that corporate innovations produce technological spillover. "We like to think we're on the side of the angels," says biotech businessman Elliot Entis. His company, A/F Protein, has produced a faster-growing salmon, which requires less food than normal breeds. "As valuable traits are put into plants and animals, they will get used," he says. "Economics will win."

No doubt—but in the face of mass hunger, should a potato that is easier to fry really be a top priority? Regardless, that's one project agricultural giant Monsanto is pouring money into. —M.S.

CONTINUED FROM PAGE 58

known to shuttle genes between micro-organisms. They have even been shown to transfer genes to the micro-algae that kill fish in toxic red tides. If transgenic bacteria are released into the ocean, could viruses transport their genes to the red tides, making them even more robust?

Even if new genes don't flow into other organisms, would transgenic plants or animals act as "exotics"—organisms imported from one ecosystem to another? The fire ant, boll weevil, and kudzu vine were all transferred to the United States where, freed from their native ecological controls, they have caused extensive damage.

To prevent such harm, regulators require genetically engineered organisms to be tested in the field—but that can create its own problems. With livestock and fowl, the tests don't pose much danger: Since the animals are kept penned in, they are unable to spread their new genes and affect the ecological balance. Fish often escape their coastal pens, so genetically engineered ones could mate in the wild, possibly creating a breed that would break out of its biological niche and disrupt the ecosystem. Landlocked farming tanks could solve this problem, but plant pollens can't be so easily contained.

Out of the world's 18 most pernicious weeds, 11 are sexually compatible with commercial crops. And researchers have demonstrated that new genes can be spread in the field from crops to weeds. Genes for resistance to pests or herbicides could fortify weeds, which already cause crop damage of $4.6 billion a year in the U.S. alone. A recent article in *BioScience* cautions, "Containment of genes from commercially grown crops will be difficult if not impossible after transgenic plants are available to the general public."

If containing plant pollen is difficult, controlling insects is next to impossible. The University of Florida's Marjorie Hoy conducted the first U.S. field test of a transgenic mite, a bug no bigger than the dot over an *i*. Mites can't fly, don't migrate very far, and can't survive the rainy summer in Florida, where the tests took place. Still, the test plot was ringed with a border of barren ground and sticky traps. Researchers wore lab coats in the plot and sprayed their hands with alcohol when they left. And after the experiment, says Hoy, "we gathered everything up in big plastic bags," including the plants and the pots they were in, and baked them in a sterilizing oven.

She wonders how tests could be safely conducted with insects that fly, such as the mosquitoes being engineered so they can't transmit malaria. "The goal is to do good," she says, "but I'm not sure they realize all the ecological issues." Maybe, she speculates, field tests could be conducted "on an island, or in giant field cages, or in a place where they can't survive the winter."

But none of those strategies would work for viruses or bacteria, which cannot be contained once they are released. That's one of the reasons Alan Wood, a senior researcher at Cornell University's Boyce Thompson Institute for Plant Research, objected to field tests of American Cyanamid's pesticide virus boosted with the scorpion-venom gene. When Wood tested the wild virus, "we could detect it up to a quarter of a mile from where we sprayed it." The virus was carried by the wind and landed on plates Wood had erected around the site. "We put insects on the plates," he says, "and they got infected." Moreover, "once the virus is in the soil, it remains there for long periods of time." How long? "Decades."

Despite all this, if the transgenic virus had just killed faster, as it was designed to do, Wood would not have objected to the trials. But the engineered virus also seemed able to infect some insects more easily than the natural virus. "Now, that shouldn't have been," says Wood. "Something else must have changed in that virus." He wasn't worried about humans getting sick—insect viruses don't infect mammals—but unleashing a virus that is both more deadly and more contagious in some insects could have major ecological consequences.

Wood is no radical environmentalist. "I want to promote this business," he says flatly. "But if you can't answer something, I'm not going to let you shoot the rest of us in the foot." Despite Wood's protests, the field tests went ahead—and, apparently, nothing bad happened.

"I really can't give you an example of serious adverse effects" that have occurred in field trials, says Colwell, who twice chaired the Environmental Protection Agency's biotechnology advisory board. While Wood agrees, it is precisely such reassurances that scare him. He sees a growing "familiarity" with biotechnology that is breeding regulatory complacency: The test of the scorpion-venom virus "would never have happened 10 years ago," Wood declares. "There's also lots of pressure from Republicans in Congress who want to get this stuff to market."

The Department of Agriculture no longer requires a permit to test certain crops that have acquired a testing track record, just a notification. And the Food and Drug Administration has never required transgenic foods to be labeled as such, even though there is a remote possibility of transferring allergies. (In one case, scientists transferred a gene from the Brazil nut to soybeans, and the soybeans caused Brazil-nut allergies.)

"I have no fears," says the USDA's Young, who oversees the regulation of transgenic invertebrates, "because I'm in a position to say, 'No, you will not let this out.' " And Zilinskas points out that genetic engineers are altering "only one or two genes." But, he says, modern commerce constantly moves whole species from one environment to another: "Every time a boat flushes its bilge, we transfer exotics" into our environment.

What's more, there are dangers to *not* pursuing biotechnology—such as millions dying of starvation. "There is no safety in this world," says Yale biotech expert Frank Richards. "There is only the balancing of risks."

"People are always getting alarmed about things getting out of control," says Richards, "but the production of life is out of control to start with. It's not an orderly process."

Scientists used to believe that evolution occurred by the gradual accumulation of single mutations. But researchers now realize that sudden, major changes in DNA also happen.

CONTINUED ON PAGE 62

IS IT KOSHER?

IF A PIG GENE were transferred into an apple, would the fruit be kosher?

"It is a cutting-edge question," sighs Rabbi Yisroel Saperstein, a rabbinic adviser at Kof-K Kosher Supervision. But, noting that genes are microscopic, he says, "It could be that one gene doesn't contain the identity of a pig." Therefore, "the consensus presently" is that such an apple would be kosher.

Rabbi Menachem Genack of the Orthodox Union agrees. With Talmudic exactitude, he notes that genetic engineers would not transfer the pig gene directly into the apple. Instead, they would clone it first. Since the gene that would actually be transferred into the apple would merely be "a copy of the pig gene, it's not a problem."

As for Roman Catholic meatless Fridays, the Vatican did not return phone calls from the *Voice*. —M.S.

SCHOOFS

CONTINUED FROM PAGE 61

"The ability to do genetic engineering—to cut and splice and rearrange DNA—is natural," says University of Chicago microbiologist James Shapiro. "So the idea that we have violated some fundamental barrier by doing genetic engineering is not correct. Whether it's safe or not, it's already going on in nature all the time." The difference, of course, is that now humans are steering and pushing nature.

The unintended consequences of playing God are one fear, but there is a far worse nightmare: playing the devil. If terrorists spliced the botulinum toxin into common bacteria such as *E. coli*, says Colwell, they could kill thousands of people. Iraq's biological-weapons program has made headlines, but as many as 17 nations—including China, Libya, and Taiwan—are believed to be developing or stockpiling biological weapons, according to the *Journal of the American Medical Association.* It noted that the Aum Shinrikyo cult, which attacked the Tokyo subway system with sarin gas in 1995, "had allegedly launched three unsuccessful biological attacks in Japan using B anthracis and botulinum toxin and had sent members to the former Zaire during 1992 to obtain Ebola virus for weapons development."

Biotechnology has existed since the advent of farming and the breeding of animals. "We have poodles and Pekingeses," says USDA geneticist Caird Rexroad, "and they were all bred from a wolflike ancestor that is very different from the dogs walking the streets of New York City."

Indeed, old-fashioned breeding has produced astounding results. Farmers have created turkeys that cannot mate because their oversize breasts—created out of the desire for better Thanksgiving meals—prevent them from getting close enough to copulate. And it was standard breeding that produced the high-yield crops of the green revolution—an achievement Charles Arntzen, developer of the edible vaccine, insists "is at least as profound as moving genes between species."

Yet even Arntzen concedes that "our ability to manipulate living beings" has accelerated tremendously over the last 50 years—an eye blink in historical terms. "All of a sudden," he says, "we have this capacity to change life forms around us. It's an awesome period of time in our history." The ability to directly manipulate DNA is the culmination of that history, for the simple reason that DNA is the blueprint for every living organism. Genetic engineering, says the University of Maryland's Colwell, "is akin to the printing press, the steam engine, the splitting of the atom, and the computer."

Humans have always wanted to change life, to mold it and make it plastic to our touch, and we could do so within the strict confines of a species. Every shade of vermillion has been bred in a rose—but never a shadow of blue. Now, however, the "natural world" of living beings, the very form and function of creatures, will become ever more subject to human mastery. The wall between technology and life has crumbled. For better or worse, genetic engineering is the ultimate taming of the wild world—the end, quite possibly, of nature. V

Part Six: Genetics and Medicine

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